Investigation of levels of oxidative stress and antioxidant enzymes in colon cancers

Kolon kanserlilerde oksidatif stres ve antioksidan enzim seviyelerinin incelenmesi

Oxidative stress and antioxidant enzymes levels in colon cancers

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Öz

Amaç: Serbest radikaller dejeneratif hastalıkların gelişmesinde anahtar rol oynarlar; buna karşın zararlı reaktif moleküller vücut içerisinde doğal korunma mekanizması ile kontrol edilebilirler. Bu çalışmada, kolon kanserli hastaların kan serumu örneklerinde süperoksit dismutaz (SOD), glutatyon redüktaz (GSH), glutatyon peroksidaz (GSH-Px) ve malondialdehit (MDA) enzim aktivitelerinin incelenmesini amaçladık. Gereç ve Yöntem: Bu geriye dönük çalışma, kolon kanseri teşhisi konulmuş hastaları (n=25) ve yaş- ile cinsiyet uyumlu kişilerden oluşan kontrol grubunu (n=25) kapsamaktadır. SOD, GSH, GSH-Px ve MDA serum düzeyleri spektrofotometrik metodlar kullanılarak analiz edildi.Bulgular: SOD, GSH, GSH-Px ve MDA enzim düzeyleri kontrol grubuyla karşılaştırıldığında istatistiksel olarak anlamlı ölçüde farklı ($p<0.05$) bulundu. Yine kontrol grubu ile karşılaştırıldığında, SOD, GSH ve GSH-Px düzeylerinde düşüş bulunurken, MDA düzeyinde anlamlı bir artış ($p<0.05$) bulunmaktadır. Kolon kanserli hastalarda SOD, GSH ve GSH-Px içeren antioksidan enzim aktiviteleri anlamlı olarak düşük iken, MDA düzeyleri ise bu hastalarda anlamlı olarak yüksektir, kontrol grubu ile karşılaştırıldığında ise durum aynıdır ($p< 0.05$). Tartışma: Öncelikle, çalışmamız kolon kanseri, oksidatif stress ve antioksidan parametreleri arasında ilişki bulunduğunu belirtmektedir. Bu çalışma yine literatürde oksidatif stress düzeylerini ve SOD, GSH ve GSH-Px gibi antioksidan enzim düzeylerini inceleyen ilk çalışmadır. Buna ek olarak, GSH-Px aktivitesindeki düşüş, MDA sentezinin artması sonucunu doğurarak, serum SOD, GSH, GSH-Px ve MDA düzeylerinin kolon kanserinin etyopatogenezine etki edebileceğini belirtmektedir.

Anahtar Kelimeler

Kolon Kanseri; Antioksidan Enzimler; Lipid Peroksidasyonu

Abstract

Aim: Free radicals play a key role in the development of degenerative diseases, none the less, effects of harmful reactive species can be controlled by natural defense mechanisms in the body. In this study, we aimed to investigate enzyme activities of superoxide dismutase (SOD), glutathione (GSH) reductase, glutathione peroxidase (GSH-Px), and malondialdehyde (MDA) in blood serum samples of patients with colon cancer. Material and Method: This retrospective study included patients diagnosed with colon cancer (n=25) and age- and sex-matched healthy individuals as the control group (n=25). Serum levels of SOD, GSH, GSH-Px, and MDA were analyzed using the spectrophotometric method. Results: Enzyme levels of SOD, GSH, GSH-Px, and MDA were found to be statistically significantly ($p<0.05$), compared to the control group. There was a significant increase in the MDA levels ($p<0.05$), whereas the SOD, GSH, and GSH-Px levels decreased in the patients with colon cancer, compared to the control group ($p<0.05$). MDA levels were significantly higher in the patients with colon cancer, while antioxidant enzymes including SOD, GSH, and GSH-Px activities were significantly lower in these patients, compared to the control group ($p< 0.05$). Discussion: Our study, for the first time, suggests a relationship between colon cancer, oxidative stress, and antioxidant parameters. This is also the first study to investigate the levels of oxidative stress levels and antioxidant enzymes such as SOD, GSH, and GSH-Px activities in the literature. Also, decreased GSH-Px activity may increase MDA production, suggesting that serum SOD, GSH, GSH-Px and MDA levels can affect the etiopathogenesis of colon cancer.

Keywords

Colon Cancer; Antioxidant Enzymes; Lipid Peroxidation

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Introduction

The etiology of cancer is multifactorial with bacteria and viruses, radiation to heredity, environmental factors, and feeding habits which are all blamed in the development of the disease [1].

Colon cancer is the third most common type of cancer in the world. About 1.2 million new cases and 608,000 related deaths are being reported annually [2]. In men, it is the second most common cancer, following prostate cancer, in terms of incidence, and it is the third most common cancer, following breast and cervical cancers in women [3]. Several risk factors such as advanced age, sedentary lifestyle, and unhealthy dietary habits have been suggested in the development of colorectal cancer [4].

However, a little development has been achieved in five-year survival rates during the past three decades in the treatment of colon cancer, despite all efforts [5].

Oxidative and nitrosative stress can also play a role in the development of colon cancer, as in other types of cancer [6, 7, 8]. Oxidative stress which is caused by an imbalance between free radical production and antioxidant defenses produces free radicals. These free radicals, in turn, induce a chain reaction. A chain reaction within the cell, in turn, leads to the deformation of the cells or cellular death. Oxidized cells are already transformed into another form by being mutated [8, 9].

-To illustrate, the formation of 8-oxodG in DNA leads to G → T transversions during replication, unless the damage is repaired by base excision repair [10].

Malondialdehyde (MDA), which is produced by the oxidation of polyunsaturated fatty acids, is one of the major parameters of lipid peroxidation [11]. For living organisms, to maintain their structural and biochemical functions, there is a constant equilibrium between pro-oxidants and antioxidants, which should be controlled continuously. The loss of the equilibrium on behalf of pro-oxidants may lead to oxidative damage. [12, 13].

Antioxidant molecules prevent potential chain reactions and other oxidative reactions by eliminating free radicals, by oxidizing themselves [13]. It has been shown that, in patients with colorectal cancer, levels of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and glutathione (GSH) reductase increase, compared to the surrounding intact tissue, and GSH decreases with increasing tumoral stage [14].

Glutathione is a tripeptide which can be synthesized in the liver using no genetic information. It is a major antioxidant which protects cells from oxidative damage by reacting with free radicals and peroxides [15]. Glutathione exists in tissues in two different types which stay in balance in tissues: reduced GSH and oxidized glutathione (GSSG). Intracellular GSH is transformed into the GSSG by a selenium-containing enzyme glutathione peroxidase. [16]. Oxidized glutathione (GSSG) reduces the oxidized form of GSH by an NADPH-dependent flavoenzyme GSH reductase [17].

Glutathione peroxidase (EC 1.11.1.9) is a cytosolic enzyme which is responsible for the reduction of hydroperoxides. In erythrocytes, it is the most potent antioxidant against oxidative stress, and it also plays a central role in phagocytic cells [18].

These pathological conditions can be prevented by the enzyme GSH-Px, while cellular functions proceed completely. In case of adequate levels of GSH-Px activity, cells are more resistant to oncogenic substances. Clinical studies have also demonstrated that GSH-Px protects kidney, liver, and pancreas from necrotic degeneration [19].

Superoxide dismutase (EC 1.15.1.1) is the metalloenzyme which catalyzes dismutation of superoxide anion radicals to molecular oxygen and hydrogen peroxide. It is found in all cells which metabolize oxygen. It is an important defense against oxygen toxicity. The main function of SOD is to protect aerobic organisms against harmful effects of superoxide [20].

In the present study, we aimed to investigate enzyme activities of SOD, GSH, GSH-Px, and MDA and to identify oxidative damage in patients with colon cancer.

Material and Methods

Specimens

A written informed consent was obtained from each participant. The study protocol was approved by the local Ethics Committee (Date: 18.04.2014/No: 03). The study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 25 patients who were admitted to Yuzuncu Yil University, Faculty of Medicine, Department of Medical Oncology and were diagnosed with colon cancer between April 2014 and August 2015 were retrospectively analyzed. The control group consisted of 25 age- and sex-matched healthy individuals based on the following criteria: eating habits, age, body weight, sex, and nonsmoking status. All patients were at an early stage of colon cancer and did not use alcohol, cigarette, or any other medication (antioxidant medications), and had no accompanying metabolic disease. The mean age of the patients and healthy controls was 40.70±4.3 and 41.32±2.3 years, respectively. The body mass index of the patients and healthy controls was 22.56±1.70 kg/m2 and 23.67±2.53 kg/m2, respectively.

Blood collection

Venous blood samples were collected early in the morning following 9-12-hour fasting from all participants. The samples were centrifuged for 10 min at 5,000/rpm/min, and serums were separated. Serum samples were kept at -20°C and activity of SOD, GSH-Px, reduced GSH, and MDA determined using the spectrophotometric method.

Measurement of serum superoxide dismutase

The SOD levels were measured using a commercial kit of brand Randox (İngiltere, SD125). The principle of the assay was based on the method of Williams et al.,1983. The enzyme activity was measured based on the alterations in absorbance at 505 nm. The results were recorded in U/mL.

Measurement of serum lipid peroxidation

The GSH-Px levels were measured using a commercial kit of brand Randox (England, SD505). The principle of the assay was based on the method of Paglia and Valentine, 1967. The enzyme activity was measured based on the alterations in absorbance due to decreased NADPH at 340 nm. The results were recorded in U/L.

Measurement of serum reduced glutathione

The GSH reductase levels were based on the formation of yellow-color due to the reaction of sulfhydryl groups found in erythrocytes with DTNB (5',5'-(2-ditiobis nitrobenzoic acid). The measurement was performed via spectrophotometry at 412 nm [23]. The results were recorded in mg/dL.

Measurement of serum lipid peroxidation

The MDA levels were measured by its transformation into a colorful form with thiobarbituric acid [24]. The absorbance was recorded in spectrophotometry at 532 nm. The results were recorded in µmol/L.

Statistical analysis

Statistical analysis was performed using the SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). The data were expressed in mean ± standard deviation (SD) using the Microsoft Excell software (Microsoft Inc., Redmond, WA, USA). The Student t-test was used to analyze the significant differences between the groups. A p value of <0.05 was considered statistically significant.

Results

The demographic and clinical data of the patient and control groups are shown in Table 1. There were no statistically significant differences in age and BMI values between the patients with colon cancer and healthy controls (Table 1).

Values expressed in mean±SD. SD: Standard deviation NS:Non-significant.

The SOD, GSH, GSHPx, and MDA values of the patient and control groups are presented in Table 2. There was a statistically significant difference (p<0.05) in the enzyme activity of SOD, indicating higher values in the patient group (159.1 ± 4.662 U/ mL), compared to the control group (79.27 ± 2.836 U/mL). Also, there was a statistically significant difference (p<0.05) in the enzyme activity of GSH-Px, indicating higher values in the patient group (20.61 ± 4.060 U/mL), compared to the controls (0.9242 ± 0.1174 U/mL). The reduction in GSH levels were higher and statistically significant (p<0.05) in the patient group (0.005270 ± 0.0002454 mg/dL), compared to the control group (0.02818 ± 0.005355 mg/dL). The MDA levels were higher (p<0.05) in the patient group (3.556 ± 0.1032 µmol /L), compared to the controls (0.9946 ± 0.01654 µmol/L) and the difference was statistically significant.

Values expressed in mean±SD. Significant, *p<0.05.*

SOD, superoxide dismutase; GSH, glutathione; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

Table 1. Demographic characteristics of patient and control groups.

Variable	Control (n=25)	Patients (n=25)	p-value
Age (years)	40.70±4.3	41.32±2.3	NS
Body mass index (kg/m^2)	23.67±2.53	22.56±1.70	NS

Table 2. Levels of SOD, GSH, GSHPx, and MDA in patient and control groups.

Variable	Patient group (n=25)	Control group (n=25)	p-value
SOD (U/mL)	159.1 ± 4.662	79.27 ± 2.836	(p<0.05)
GSH-Px (U/mL)	20.61 ± 4.060	0.9242 ± 0.1174	(p<0.05)
GSH (mg/dL)	0.005270 ± 0.0002454	0.02818 ± 0.005355	(p<0.05)
MDA (µmol/L)	3.556 ± 0.1032	0.9946 ± 0.01654	(p<0.05)

Discussion

Free radicals are extremely reactive molecules which carry unbound electrons [25, 26]. Due to their chemical features, they react with cellular structures such as lipid membrane, protein, carbohydrate, and DNA, thereby, leading to damage. In recent years, these radical substances were considered responsible for etiologies of many diseases [18, 27, 28, 29].

Impairments in DNA repair causes various types of cancer, such as breast, colon, and skin and they also cause abnormal growth and brain abnormalities [30]. Fortunately, the human body has a system which can recognize free radicals and inactivate them. This system, which is composed of enzymes and antioxidants, attracts, and binds free radicals, before they attack the cell membrane, nucleic acids, and cellular components [31, 32]. Antioxidant defense is primarily provided by three antioxidant enzymes: SOD, catalase (CAT), and GSH-Px. The GSH reductase is one of the first-degree enzymes, while glucose-6-phosphate dehydrogenase (G6PD) is one of the second-degree enzymes [33]. In case of inadequate antioxidant capacity of the organism metabolic reactions become harmful for cells, and this unpreventable harmful alteration leads to the development of different types of malignancies [34]. Enzymes containing low-molecular weight antioxidants (SOD and GSH-Px) and redox system containing low-molecular weight antioxidants may disrupt the equilibrium, which accelerates the progression of the disease [35, 36].

A series of mechanism which may lead to oxidative stress exists in cancer patients [37]. Depending on oxidative stress; lipids, proteins, enzymes, carbohydrates, and DNA can be damaged, thereby, leading to damage in membranes, random breakages and bonds in the DNA chains, and damaged enzymes and structural proteins may result in cellular death, which forms the molecular basis for the development of cancer, neurodegenerative and cardiovascular diseases, diabetes, and autoimmune disorders [33, 38].

Several studies have shown alterations occurred in the natural antioxidants (such as GSH) in the organisms. Glutathione peroxidase participates in the elimination of hydrogen peroxide. Selenium comprises an important part of GSH-Px. Enzyme activities of GSH and others are used in the determination of altered antioxidant status in the organism [39]. Also, it has been suggested that mucosal oxidative stress plays a key role in the development of colorectal cancer. The ROS in colonic lumen also has a direct genotoxic effect and lead to the formation of fecal mutagens [39]. This can be attributed to the oxidized food residues, increased iron ions, oxidants, toxins, bacteria, and bile acids [40, 13, 41, 42].

In previous studies, the MDA levels in tumoral tissue and serum increased in cancer patients [43, 44]. In the present study, we also found a significant increase in the MDA levels in the patients with colon cancer, compared to the control group, (p<0.05). However, we were unable to compare the studies done previously on MDA in colon cancer, although we compared other types of cancer. Therefore, we believe that our study, which suggests that free oxygen radicals and oxidative stress can play a role in tissue damage in colon cancer, would contribute to the existing literature. Also, we found a statistically significant increase in the MDA levels and a significant decrease in the

GSH levels in the patients with colon cancer, compared to the healthy controls. Low GSH levels in cancer patients may result from increased toluene sulphonic acid (TSA) concentrations. The reason of this is that GSH can be used in the synthesis of sialic acid (SA). Decreased GSH levels in the patients with colon cancer, compared to the healthy controls. Low GSH levels in cancer patients may result from increased toluene sulphonic acid (TSA) concentrations. The reason of this is that GSH can be used in the synthesis of sialic acid (SA). Decreased GSH levels can also be explained by increased MDA levels, which are the indirect indicators of oxidative stress [45]. Hoffman et al. reported that the GSH-Px activity remained unchanged in patients with colorectal cancers. Masotti et al. showed that enzyme GSH-Px protected the cells from damage of lipid peroxidation, particularly in membrane. Peroxy-polyunsaturated fatty acids are transformed into hydroxyl-fatty acids via enzyme GSH-Px using GSH, instead of short-chain fatty acids and MDA production [42]. As a result, decreased GSH-Px activity may lead to increased MDA production. Our study results are consistent with previous findings which reported a considerable increase in the GSH-Px activity in human colorectal cancer [13,41,42,47,48].

Oxygen radicals play a major role in the protection of cells against oxidative stress. The relationship between the antioxidant status and the main markers of oxidative stress (i.e., lipid peroxides and oxidized proteins) indicates an improved health index and stance [49]. In a study, serum MDA levels were found to increase in patients with colon cancer, and cardiac disease, and MDA, SOD, GSHPx, and GSH were increased in a study which they conducted with patients with colon cancer and GSH were increased [13,49]. In patients with colon cancer, biochemical analysis is also important, as oxidative stress severely affects biochemical parameters in colon cancer. Therefore, we can conclude that increased MDA levels suggested that oxidative stress played a role in colorectal carcinogenesis, since increased MDA, a lipid peroxidation product, can severely affect and change the disease prognosis in colon cancer. Survival or recovery of the patient from colon cancer is likely to decrease MDA levels, thereby affecting the disease prognosis positively. As MDA is an oxidative stress indicator, it can be used in the clinical follow-up of patients with colon cancer. Our study results are also consistent with the previous studies of Rainis et al. (2007), Skrzydlewska et al. (2005), Nayak et al. (2005), and Kaya et al. (2010).

Canbolat et al. showed that serum activity of SOD enzyme was higher at the preoperative period, compared to the postoperative period, in patients with laryngeal cancer in another study. Increased concentrations of superoxide and hydrogen peroxide may increase the SOD activity in cancerous tissues [49]. In the present study, increased SOD level measurement suggested that oxidative stress played a role in colorectal carcinogenesis. These results are also consistent with previous study findings [44, 45, 48, 49, 51].

In conclusion, our study shows that free oxygen radicals and oxidative stress play a major role in tissue damage in colon cancer. In addition, increased MDA levels in patients with colon cancer indicate oxidative stress, suggesting that oxidative stress plays a key role in the carcinogenicity. Decreased in GSH-Px activity may increase MDA production; as a result, serum SOD, GSH, GSH-Px and MDA levels can affect the etiopathogenesis of colon cancer.

Decreased antioxidant enzymes and increased oxidative stress suggested a strong relationship between oxidative stress and colon cancer. Therefore, we suggest that oxidative stress increases in colon cancer, thereby, disrupting the healing process and decreasing oxidative stress can yield favorable outcomes in these patients.

Compliance with ethical standards

This original study was conducted as a research program of the Project for Development of Institute of Sciences of Yuzuncu Yil University.

Competing interests:

The authors declare that they have no competing interests.

Ethical approval:

Ethical approval for this retrospective study was obtained from the institutional review board of Yuzuncu Yil University.

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